Good afternoon, and welcome to Scientific Sessions 2012. It is my privilege and honor to address this esteemed group of researchers, clinicians, colleagues, and friends. I thank you for being here today and for your commitment to science and to the fight against cardiovascular diseases and stroke.

I’d like to extend a heartfelt welcome to all of you who are young investigators and early in your careers. I feel a special bond with you today. It was 25 years ago, just down the road in Anaheim, when I presented an oral abstract at Scientific Sessions on my very first independent research study.

I am honored to be back here today as the president of the American Heart Association. I also stand before you today as a nurse, a basic scientist, and an epidemiologist. This unique career journey has enriched me with the opportunity to work alongside many of you in many capacities. More importantly, I have been able to care for patients, pursue scientific discovery, and study population health, all with the goal of saving and improving lives.

Today, I will discuss a major global threat to human health: hypertension. Almost 1 billion people have high blood pressure, putting 1 of every 7 people on the planet at higher risk of cardiovascular diseases and stroke. The World Heart Federation projects that number to grow by >50% by the year 2025. As you know, here in the United States, nearly 1 in 3 Federation projects that number to grow by >50% by the year 2025.

Today, I’ll discuss the urgent need to do everything in our power to change this disturbing picture, both through continued genomic research and drastic environmental change. Hypertension is a global pandemic, and we will need bold solutions to solve it.

I became interested in the field of genetics while caring for patients as a clinical research nurse at a VA hospital. I was overseeing randomized clinical trials in hypertension, and I was fascinated by the considerable variability among patients, not only in response to blood pressure–lowering drugs but also in response to hypertension itself.

Some patients would have severe left ventricular hypertrophy (LVH) at low levels of untreated blood pressure. Others would have no hypertrophy even with very high blood pressure levels. I became keenly interested in the “why” of variability.

I began to explore that question and found that blood pressure variability predicted the degree of increased left ventricular (LV) mass. But the variability was still unexplained. And so it struck me that there must be other factors, possibly genetic, that led to this variation in blood pressure and in target-organ damage.

My interest in genetics was further fueled by my observation of patients who passed by my VA office on their way to their dialysis treatments 3 times a week. Nearly all were African Americans, a statistical oddity that made me question whether something unique was causing renal failure in this population. I had directly observed higher blood pressure levels and more LVH in my African American patients, but I wondered: Was a genetic component predisposing them to higher blood pressure and multiple sequelae?

Since asking that question 25 years ago, genomics technology and genomics knowledge have exploded. Our ability to approach the genetics of hypertension was limited then. Much of the work involved quantifying the amount of variation in a genetic trait attributable to familial relationships. We knew that hypertension was more common in individuals with a strong family history of hypertension.

And in my research in the Hypertension Genetic Epidemiology Network (HyperGEN) LVH study, LV mass was strongly heritable, particularly in African Americans. Data from another study show that up to 70% of the variation in LV mass among African American siblings is explained by familial relationships, but which genes were responsible could not be determined by this method.

These answers had to wait for the discovery and annotation of millions of genetic variations through the Human Genome...
Completed nearly a decade ago, the genome project was an incredible effort: It sought to identify all of the ≈22,000 protein-coding genes in human DNA and to determine the 3 billion chemical base pairs that make up the human DNA sequence. The Human Genome Project provided the tools for identifying genes that contribute to rare forms of extremely high or low blood pressure, among many other diseases. However, the search for the genes contributing to essential hypertension has proven more difficult.

As information about the human genome has expanded (and continues to expand), promising new kinds of studies for gene discovery have emerged. One technique used to study genetic variation among individuals, the genome-wide association study (GWAS), was named “breakthrough of the year” in 2007 by *Science*. GWAS offers the opportunity to search the genome in an agnostic way for any genes that contribute to hypertension.

The GWAS has complemented our traditional approaches for gene discovery by capturing both known and novel genes, including those with only modest effects on blood pressure. The GWAS methods have yielded an unprecedented number of discoveries; significant genetic associations across multiple diseases can be found on every chromosome.

Essential hypertension has been thought to result from common genetic variations, called polymorphisms, with moderate effects on blood pressure. To identify these genes, a large number of genetic markers are required. Technology evolved such that gene “chips,” which actually share some technologies with computer chips, are now available. These chips characterize millions of polymorphisms across the genome to enable the identification of a causal genetic variant.

The success of GWAS also depends on a large sample size. The most comprehensive blood pressure GWAS study done to date included >200,000 individuals. In this GWAS study, 22 of the 28 significant genes would never have been considered as important for blood pressure. This demonstrates the unique power of this kind of study: This agnostic approach allows us to better understand the pathophysiology of hypertension, and that can lead to novel antihypertensive treatments.

Our laboratory performed a GWAS for LVH in hypertensive African American families during the second phase of the HyperGEN LVH study. We found a region on chromosome 11 that was associated with LV wall thickness; the most significant polymorphism lies within the promoter of the NCAM1 gene.

NCAM1 is a glycoprotein that mediates adhesive interactions between cells in the nervous system and in muscle. Animal studies suggest NCAM1 is important for LVH in the context of hypertension. Further studies are needed to elucidate the mechanisms by which NCAM1 influences hypertrophy, this finding once again highlights the promise in the GWAS approach.

While GWAS have focused mostly on *common* polymorphisms, evidence is accumulating that *rare* mutations are also important. Fortunately, it is now feasible to sequence the entire genome or the protein-coding part of the genome, known as the exome, to identify these variants. These new sequencing methods have already identified new genetic mutations underlying a rare hypertension syndrome.

We used the exome-sequencing method in the HyperGEN study to identify genetic variants for LVH, but we combined our exome-sequencing approach with a complementary method using human induced pluripotent stem cell–derived cardiomyocytes. Our sequencing study revealed a large number of genetic variants for LVH—too many to sort through to understand which might be important. So we induced hypertrophy of cardiomyocytes using isoproterenol. We compared the expression of proteins in those cardiomyocytes to “control” cells. From our list of hundreds of genes from the families, we found 44 that are differentially expressed in human cardiomyocytes in our model system.

I am thrilled about the potential of these genomic findings and in our ability to translate these discoveries in humans back into the laboratory to understand the disease mechanisms. I firmly believe that one day a detailed understanding of which variants and genes are involved in essential hypertension, LVH, and even renal failure (and how they are involved) will lead to new and better prevention, diagnosis, and treatment options.

But those will be the future lessons of genomics. What are today’s lessons, and how can we use them? As an epidemiologist, I am compelled to ask what we can do now about the pandemic of hypertension.

One undeniable message in the hypertension genetics literature is that most polymorphisms have very small effects on blood pressure. But when we’re talking about the high prevalence of hypertension, the most important factor may not be the polymorphisms themselves but how they interact with the external environment. And this is what is so important to understand: While our genome has evolved over thousands of years, our environment has evolved quite dramatically over a very small window of “genomic” time.

It is the intersection of our genome and this new environment that is critically important to the epidemic of hypertension. We know many of the environmental contributors to...
hypertension: high dietary sodium intake, physical inactivity, and obesity, to name a few. And so the lesson in today’s genetics is this: We must do everything possible to understand and ameliorate the effects of the environment on hypertension.

Think about physical activity. Hundreds and hundreds of generations stayed in shape because they had to. Getting away from a saber-tooth tiger or woolly mammoth required humans to stay physically fit. And if you wanted to do anything or go anywhere, you had to walk or run. Then, just a short time ago, in genomic terms anyway, we had cars. Then, again very suddenly, we were flying. As a result, we became less active. We are now people who sit, and we sit a lot, whether we are at home, at work, or at play.

Meanwhile, our inactive populations are now eating in a way that was unimaginable even decades ago. Mass food production started in the late 19th century.22 Within a half century or so, diets around the world changed dramatically. Processed, packaged, and restaurant foods became increasingly popular. By the 1970s, the family-prepared dinner was largely replaced by larger portions packed with excess sodium, often washed down with sugar-filled drinks.24

Think about it this way: Our genome has evolved in a low-sodium, high-activity environment over 8000 generations. Yet the dramatic shifts in dietary sodium and physical inactivity have occurred in just 4 generations.25

Everyone in this audience has seen the results of the interaction between our genome and the new environment. I can’t possibly discuss all the cardiovascular consequences, so instead I’ll focus only on one important determinant of hypertension: sodium consumption. Sodium is so prevalent in processed and restaurant foods that we get >75% of the sodium in our diets this way.26

The average American consumes about 3400 mg of sodium every day,27 more than double that recommended by the American Heart Association.28 We know from a meta-analysis of sodium reduction trials that even modest reductions in sodium result in a 5-mm Hg decrease in systolic blood pressure among patients with hypertension.29 We also know that for every 5-mm Hg reduction in blood pressure, we will have 14% fewer deaths from stroke and 9% fewer deaths from heart disease.30

Still, I’m hopeful about our future. That’s partly because of our genomics accomplishments. We are getting more and more information about genes that are important for essential hypertension, and we’re going to get even more as human genome research continues. This knowledge can be crucial to our efforts to build a healthier environment and to personalize hypertension treatments.

Although we can’t change our genome, I passionately believe that we can change our environment. As scientists, healthcare providers, and educators, we have proven we can effect change on a grand scale. Our record shows that we are very good at overcoming major difficulties. And we are at a very promising starting point: We already know a great deal about how our environment contributes to hypertension.

Now, we need the will and innovation to put that knowledge to work. That’s really all that happened when we accomplished one of the greatest feats in science, landing on the moon in 1969. President Kennedy told Congress, just 8 years earlier, that we would land a man on the moon and return him safely to Earth within a decade. Then scientists carried out that will, discovering and innovating and eventually reaching that goal.

In an example from medicine, that’s how we eradicated smallpox by 1980.31 We had the will; we developed the vaccine; and, importantly, we found creative ways to deliver the vaccine around the world.

In much the same way, we must find the population interventions to prevent hypertension in those who are genetically susceptible and to identify all hypertensive people and get them treated. We need to be sure that the many effective medicines we’ve already developed, and those we will develop, can be used to benefit those individuals.

And we need to continue our search for genetic polymorphisms that can help to personalize medicine for each individual’s genome. There’s no reason why we can’t prevent hypertension for many and effectively control high blood pressure for most of the 1 billion people with hypertension around the world.

Here’s just one illustration of how we can change this picture in communities everywhere. It’s a program in North Carolina called “CheckIt, ChangeIt,” which helps people get blood pressure screenings and understand them.32 This is a great example of collaboration because it involves the American Heart Association, as well as partners from business, education, and government.

As we look for hypertension solutions, we need to apply that same vigor and excitement that we did with the Human Genome Project and the eradication of smallpox. As you recall, those 2 projects galvanized the world. We need to once again galvanize the world to change.

The solution must be many things, and everyone here has the potential to be part of it. Although as scientists, we are all trained to know the “right next question,” that is difficult with such a complex population-based problem. So my first challenge to you today is to continue to find that next question … or those next questions.

I challenge you to pursue the most innovative solutions to hypertension. There should be no limit to our investigation. Who imagined 25 years ago that we would map 22,000 human genes? Maybe we can find 22,000 environmental prevention strategies. Or maybe it will only take 22.

I urge you to pursue this innovation together. We need more collaborative work between basic, clinical, and population scientists. And we must recognize the importance of innovation outside the clinic, lab, or classroom. The solutions will not come entirely from our biomedical world. They will also come from society, business, and government. We must advocate for large-scale change by asking the difficult questions:

- How do we create a healthier food supply?
- How do we find innovative ways to mass produce and deliver not only convenient but healthy food?
- Why can’t we make the healthiest food options the most affordable?

Today, I also challenge you to do more for your communities. We all invest heavily in our careers to improve human health. But we have an opportunity to do more. We can advocate for public policy; we can share healthy-eating tips with friends and family; and we can help school kids understand nutrition and the importance of staying active. I’d like to close with the
story about why I’m here today. It is the story that inspires me every day to fight disease to save lives.

This story is about a man named Roberto.* We met in 1981 under the worst of circumstances. I was a critical care unit nurse, and Roberto was a man in his 50s who was in the middle of a massive, evolving myocardial infarction. He was grasping his chest in pain and struggling for every breath.

In the middle of it all, Roberto reached up and grabbed my arms with both hands, and our eyes met. Our faces were 6 inches apart. Roberto could barely get the words out, but I’ll never forget them. He said, “Don’t let me die.”

The chaos continued for another 10 minutes before Roberto was stabilized. We did not let Roberto die that day. He lived 3 more years, he relished with his family and friends. But his life was still too short.

I’m here today because of Roberto. And for the many people just like Roberto who are saved by you, your colleagues, your teammates, your students, and your mentors.

I know each of you has your own “Roberto” story. We have a tremendous opportunity to save many other people. But to do so, we must innovate, we must be creative, and we must collaborate.

Thank you for your service to human health. And thank you for your time today.

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References

*Pseudonym.


Transforming Cardiovascular Health Through Genes and Environment: Presidential Address at the American Heart Association 2012 Scientific Sessions

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